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Approach to diagnosis and treatment of familial hyperlipidemia

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ABSTRACT

Familial hyperlipidemia (FH) is an autosomal dominant inherited disease characterized by genetic disorders with severe high blood cholesterol levels. There are two forms of the disease which are homozygous and heterozygous FH. FH cases are generally caused by hereditorial mutations in the LDL receptor (LDL-R) gene and less commonly in genes encoding apolipoprotein B (Apo B) and pro-protein convertase subtilisin/kexin 9 (PCSK9) proteins. The risk of early-onset coronary artery disease (CAD) in FH patients is 20 times higher than the normal population. Early diagnosis and treatment of FH will greatly reduce the morbidity and mortality associated with CAD.

Keywords: Familial hyperlipidemia, heterozygous familial hyperlipidemia, homozygous familial hyperlipidemia, low-density lipoprotein receptor mutation

Familial hyperlipidemia (FH) is a common genetic disorder that causes early cardiovascular diseases and is responsible for approximately 20% of coronary artery diseases (CAD) especially seen under 45 years of age. However, the diagnosis of FH is often overlooked and patients are diagnosed after experiencing a major coronary event. Cardiovascular diseases could be significantly reduced by early diagnosis and treatment of these patients and their family members.[1]

FH is an autosomal dominant disease that is seen as a result of mutations in one or more genes that cause a significant increase in low-density lipoprotein (LDL) levels.[2] There are many mutations, but they are most common in 3 genes; 85-90% in the low-density lipoprotein receptor (LDLR) gene, 2-4% in the proprotein convertase subtilisin/kexin 9 (PCSK9) gene, and 1-12% in the apolipoprotein B (ApoB) gene.[3-5] Those who have more than one of the mutations are affected more than those who carry a single gene mutation. Homozygous individuals have very high total cholesterol levels (above 500 mg/dL) and often develop atherosclerotic cardiovascular disease before the age of 20 and death occurs before the age of 30 years.[6] The prevalence of the disease is reported at very different rates between societies, depending on ethnic differences and the diagnostic method. The prevalence is around 1 in 300 in heterozygous individuals and 1 in 300,000-400,000 in homozygous individuals.[4]

According to lipoprotein electrophoresis FH's are divided into 5 types; Type 2 FH is the most common type among these and with early diagnosis and treatment, the risk of cardiovascular disease can be significantly reduced in these people.[7, 8] Type 2 FH can be seen in homozygous and heterozygote forms. Homozygous individuals show the signs of the disease more seriously and at an earlier age than heterozygotes.

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Clinic

Individuals with homozygous FH have severe, early atherosclerotic cardiovascular disease and generally die before the age of 30 years. However, heterozygous individuals also have high LDL cholesterol levels but the signs of atherosclerotic cardiovascular disease are noticed in middle ages. Apart from cardiovascular diseases, hyperlipidemia may also cause xanthomas and xanthelasmas on the skin, arcus cornea, xanthelasmas on the eyelids, lipemia retinalis, fatty liver disease and acute pancreatitis. [9-11] Individuals with FH often have a family history of hyperlipidemia.

If a person whose LDL cholesterol level is above 190 mg/dL has a family history of hyperlipidemia and/or early cardiovascular disease, or has xanthoma in himself or a family member, or has a family history of cardiac sudden death it is necessary to search FH and make further estimation. [1]

Evaluation of FH patients

The person should be assessed primarily for atherosclerotic cardiovascular diseases and risk factors. Those with early CAD, high cholesterol and tendon xanthoma that may be associated with FH in their family should be queried. Patients should be evaluated for the findings of cholesterol storage in the skin and eye and the presence of stenosis in peripheral arteries on physical examination. LDL and total cholesterol levels are high in the lipid profile of the patients, and high-density cholesterol (HDL) levels are normal or low. Triglyceride levels are mostly normal, and high levels do not rule out the diagnosis of FH. If possible, all patients with FH should be measured for lipoprotein (a) levels, because those with high lipoprotein (a) levels have higher risk of having cardiovascular diseases.

There is no clear consensus on when genetic testing should be used in the diagnosis and the treatment of hyperlipidemia. If a patient has been diagnosed with

Table 1. Dutch lipid clinic network diagnostic criteria for FH

Criteria	Points
1) Family history	
First-degree relative with known premature (men: < 55 years; women: < 60 years) coronary or vascular disease	1
First-degree relative with known LDL-C above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis	2
Children < 18 years of age with LDL-C above the 95th percentile	
2) Clinical history	
Patient with premature (men: < 55 years; women: < 60 years) coronary artery disease	2
Patient with premature (men: < 55 years; women: < 60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL cholesterol levels	
≥ 325 mg/dl	8
251-325 mg/dL	5
191-250 mg/dL	3
155-190 mg/dL	
5) Genetic analysis	
Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Diagnosis is based on the total number of points obtained	
A "definite" FH diagnosis requires > 8 points	
A "probable" FH diagnosis requires 6 to 8 points	
A "possible" FH diagnosis requires 3 to 5 points	

FH: familial hypercholesterolemia

FH, screening of all first-degree relatives, including children above the age of two, is recommended in some guidelines. In some different guidelines recommend that genetic tests could be done if the result of test will change the clinical decision.[12-14] Mutations of LDLR, ApoB and PCSK9 genes could be screened in clinical suspicion of homozygous FH, but their normality does not mean that there are no genetic defects because there may be other rare genetic disorders. There is no clear recommendation for genetic testing in individuals with heterozygous.

Diagnosis

For the diagnosis of FH, the presence of a genetic mutation (in one of the LDLR, ApoB or PCSK9 genes) or clinical characteristic symptoms together with a high LDL cholesterol level is required. If genetic tests are not performed, some diagnostic criteria can also be used for the diagnosis of FH; Dutch Lipid Clinic Network diagnostic criteria is the one of them (Table 1).[4, 15]

Heterozygous FH can be diagnosed by genetic tests or clinical criteria. In homozygous FH patients clinical diagnosis could be made with high LDL cholesterol levels (if untreated LDL cholesterol level is above 500 mg/dL or treated LDL cholesterol level is above 300 mg/dL) or with the presence of skin or tendon xanthoma before 10 years of age, or with family history that both parents have high LDL cholesterol levels. However, LDL cholesterol levels are only a determinant in the diagnosis of FH and LDL cholesterol values below 500 mg/dL without treatment, especially in young people, do not exclude the possibility of homozygous FH.

Differential diagnosis

Hyperlipidemia, skin xanthoma and early atherosclerotic cardiovascular diseases can also be seen together with rare genetic disorders such as familial combined hyperlipidemia, familial dysbetalipoproteinemia, hyperbetalipoproteinemia, cerebrotendinous xanthomatosis, juvenile xanthogranuloma and sitosterolemia.

Treatment

The objective of FH treatment is important to reduce LDL cholesterol levels and prevent cardiovascular diseases. Lifestyle changes including diet, physical activity and weight control should be suggested to reduce LDL cholesterol levels in all patients and cardiovascular risk factors should be corrected. Although the consensus about the treatment goals and where the end line is still not clear, the first step is to reduce LDL cholesterol level by 50%. Aspirin also should be added to the treatment because almost all patients with FH are at risk for atherosclerotic cardiovascular diseases.

Statins, ezetimibe, PCSK9 inhibitors, lipid apheresis and evinacumab could be used in the medical treatment of homozygous FH. Statins are the first medical agents because of their potent in LDL cholesterol lowering efficacy and high doses should be preferred. Ezetimibe can be added to the treatment in patients who do not reach the target LDL value with high-dose statin therapy. PCSK9 inhibitors (alirocumab and evolocumab) can be added to the treatment if there is no sufficient response in patients using statins and ezetimibe. PCSK9 inhibitors can decrease LDL cholesterol levels by 30% in individuals with homozygous FH. [16] If the LDL cholesterol level is still not reduced with these treatments lipid apheresis could be used as additional treatment option. Though lipid apheresis treatment is individualized according to the patient, generally it is applied in every 2 weeks on average. With this method, a 60-70% reduction could be achieved in LDL cholesterol levels. There are many different effective apheresis techniques that can separate lipids from plasma or whole blood. American Society for Apheresis (ASFA) reports lipid treatment as a category I indication for homozygous FH and as a category II indication for heterozygous FH patients. 16 Angiopoietin-like protein 3 (ANGPTL3) is a hormone produced in the liver that inhibits lipoprotein lipase. Evinacumab, a monoclonal antibody developed against ANGPTL3 has been recently used in the treatment of homozygous FH.[17]

In heterozygous FH, treatment is also started with high-dose statins. If there is no decrease above 60% in the LDL cholesterol level measured after 6-12 weeks, 10 mg/day ezetimibe is added to the treatment. If there is no additional 20-30% decrease in the LDL cholesterol level re-examined after 6-12 weeks in the combination of high-dose statin and ezetimib, a PCSK9 inhibitor is added to the treatment. Patients whose target LDL cholesterol level is still not reached with these treatments should be switched to third-line treatments, as mentioned above for homozygous FH patients.[18]

Goal of therapy

Reducing LDL cholesterol levels in patients with FH is the main goal of treatment, but this is not

always possible. Therefore, the target value could be changed for different patients according to the cardiovascular disease risk factors in patients. The target LDL cholesterol level should be 55 mg/dL in very high-risk patients with diabetes, atherosclerosis, stage 3-4 chronic kidney disease or a previous case of CAD. A target of 100 mg/dL may also be acceptable for individuals with low risk factors.

Treatment during pregnancy

Women of childbearing age are advised to avoid pregnancy while on statin therapy. If pregnancy is planned, statin should be discontinued 3 months in advance and should not be used again until the breastfeeding period is over. Since there is no proper treatment during pregnancy, cholesterol measurement is not recommended. Lipid apheresis is the safest therapy that can be used during pregnancy.[19]

Prognosis

Prior to statin therapy, patients with FH had a very high risk of early CAD and mortality rates. With new treatment methods, there have been significant improvements in the prognosis of the patients. Nevertheless, individuals with FH are at 3 times risk of fatal and non-fatal myocardial infarction than people with similar characteristics without FH.[20]

CONCLUSIONS

Authors' Contribution

Study Conception: SU, KÇ, İBT,; Study Design: SU, KÇ, İBT,; Supervision: SU, KÇ, İBT,; Literature Review: KÇ, İBT,; Manuscript Preparation: KÇ, İBT and Critical Review: KÇ, İBT.

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